

## INFLUENZA ANTIBODIES IN THE POPULATION OF THE USA \* An Epidemiological Investigation

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### SYNOPSIS

Sera taken from persons of various ages in 1951 and collected from adults yearly from 1943 to 1951, inclusive, were tested by the haemagglutination-inhibition method with influenza viruses selected to represent the subgroups of each antigenic type. These were influenza A—WS (1933) and PR8 (1934); influenza A—prime—FM1 (1947) and FW-1-50 (1950); influenza B—Lee (1940) and IB1 (1950); influenza C—1233 (1947). The sera tested with influenza A and B viruses were treated with cholera filtrate to remove non-specific inhibitor. Since influenza C virus was not affected by the non-specific substance, the sera tested against this agent were not so treated.

Children's sera showed high antibody level, attained at an early age, for FM1 and FW-1-50 viruses, and essentially no antibody for WS or PR8. By contrast, adult sera revealed high antibody content for PR8 and moderate titres for WS and the A-prime viruses. In adult sera, antibody against the PR8 virus increased significantly in 1944, after the 1943-4 epidemic, and remained at a relatively constant level for the eight succeeding years. The antibody pattern for WS was similar to that for PR8, but the values for its titres were only half as great. Antibody against the A-prime strains rose steadily from inconsequential levels in 1943 to high mean titres in 1951. These findings were consistent with virus isolation studies which suggested that the A-prime viruses, such as FM1, were introduced about 1946 and have been continuously

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\* Certain portions of this paper were presented at the Symposium on Serological Patterns in Mass Populations: Approaches to Methods for Measuring Susceptibility of Populations to Viral Influenza (annual meeting of the Society of American Bacteriologists held on 30 April 1952 in Boston, Mass., USA), the proceedings of which have not been published.

prevalent since that time, while the WS and PR8 agents have been recovered only occasionally in recent years. Sera tested with Lee and IB1 viruses showed essentially identical titres. Antibody to these strains was low in the sera of children, indicating that there had been little previous exposure to the B agents. Adult sera showed marked elevation in titre between 1944 and 1946, and the titres have remained at a high level since that time. The increase in 1946 followed the influenza B outbreak of 1945-6; the increase in the previous year occurred in spite of the fact that there was no epidemic. Children developed significant antibody to influenza C in early life, and high antibody levels were observed in adult sera collected over the nine-year period. These observations indicate that the virus was widespread in the population and was prevalent before 1943.

Early in the study of viral influenza it was noted that the immunology of this disease conformed to the basic principles established for other infectious agents. Thus, infection is followed by specific antibody production and there is a rough but not absolute correlation between the amount of specific antibody in the circulating blood and the susceptibility or resistance of the host (Francis et al.;<sup>14</sup> Rickard et al.;<sup>40</sup> Salk et al.<sup>41</sup>). Moreover, the kind and amount of specific antibody may be used as an index of previous infection with the virus, and information regarding the past occurrence of these agents may be obtained by determining the antibody level against the various types of virus in representative samples of the population.

In the early investigations of this sort, the antibody levels were usually measured by the serum-neutralization test (Francis et al.;<sup>14</sup> Horsfall et al.;<sup>28</sup> Rickard et al.<sup>40</sup>). This method was reliable, but costly in time and material, and has largely given way to the simpler haemagglutination-inhibition test of Hirst.<sup>25</sup> Unfortunately, the value of the latter technique has been qualified because of the presence in animal and human sera of heat-stable mucoprotein substances (Hirst;<sup>28</sup> McCrea<sup>33</sup>) which inhibit haemagglutination by the influenza A and B viruses. This inhibition is non-specific, and inhibitors are often present in such quantities that they prevent agglutination at higher dilutions than do the specific antibodies. This results in false positive antibody readings.

It was found that the inhibitory activity of this non-specific factor in serum is destroyed by treatment with the filtrate of cultures of *Vibrio cholerae* rich in a substance called receptor-destroying enzyme (RDE) (Anderson<sup>2</sup>). Moreover, the recent studies by Mulder and associates<sup>36</sup> and by Tyrrell & Horsfall,<sup>47</sup> as well as unpublished investigations in this laboratory, have shown that this cholera-filtrate treatment will remove the non-specific inhibitor of influenza A and B viruses from serum without destroying significant amounts of antibody. Hence, it is now possible to measure accurately the antibody in human serum against these two

viruses by the haemagglutination-inhibition method. Recent investigations in this laboratory (Hilleman & Werner<sup>24</sup>) showed that the 1233 strain of influenza C virus was not inhibited by the non-specific factors in human serum. For this reason it is not necessary to treat the sera with cholera filtrate in order to measure the antibody against this agent.

This article describes the findings of a study made on human serum to determine the relation between the distribution of specific influenza antibody in the population of the United States of America and the prevalence of the various types of influenza in recent years. The population was sampled in two ways. The first method employed sera collected during 1951 from persons of various ages, while the second employed sera collected from representative groups of adults during each calendar year from 1943 to 1951, inclusive. Although the samples were small, the findings obtained by each of these methods were in good agreement and, moreover, were consistent with those of virus isolation studies made during the same period.

### Materials and Methods

#### *Serum*

The sera tested in this study were selected as representative of the population of the USA with respect to influenza antibody. Most of the specimens had been obtained for other purposes and had been stored for years. The sampling of the population was therefore by no means random, but, within the limits of the availability of serum, the selection could be considered reasonably representative.

All sera were obtained from military personnel or their dependants free from active respiratory disease at the time of collection. Specimens used in the tests for influenza A and B were from groups of persons different from those tested for influenza C. The children's sera<sup>a</sup> were from patients hospitalized for non-respiratory causes in the summer and autumn months of 1951. The adult sera dated prior to 1951 were from persons ill with non-respiratory disease during the summer and autumn months of the indicated year. The adult sera for 1951 were from soldiers in good health; those tested against influenza A and B were collected in August, and those used in the tests for influenza C antibody were drawn in February. All specimens were stored at  $-20^{\circ}\text{C}$  in this laboratory from the time of their collection.

#### *Cholera-filtrate preparation*

*V. cholerae* strain 4-Z was used for the preparation of cholera filtrate. This agent was obtained from Dr. B. Briody, who had received it from Sir

<sup>a</sup> We are indebted to Colonel O. C. Bruton, M.C., Chief, Pediatrics Section, Walter Reed Army Hospital, Washington, D.C., USA, for these sera.

Macfarlane Burnet. The filtrate was prepared by growing the organism for 24 hours at 35°-37°C in fresh beef-heart infusion broth containing 1% neopeptone and 0.5% sodium chloride. The pH of the medium was adjusted to 7.6 and the material sterilized in the Arnold sterilizer. This represented a modification of the original method of preparation described by Burnet & Stone.<sup>5</sup> The Seitz filtrate was adjusted to a pH of 7.0 and usually had an RDE titre of 1/256 when tested with egg-line FW-1-50 virus by the assay method of Burnet & Stone.<sup>5</sup> It was highly effective in removing the non-specific inhibitor from serum but did not destroy any significant amount of specific antibody.

#### *Cholera-filtrate treatment of serum*

All the sera to be tested against influenza A and B viruses were treated with cholera filtrate to remove non-specific inhibitor by the method of Mulder, de Nooijer & Brans.<sup>36</sup> In this procedure, each volume of serum was incubated for 14-15 hours at 37°C with four volumes of the filtrate. Residual filtrate activity was removed by heating the mixture at 56°C for 50 minutes. Under the test conditions employed, influenza C virus (strain 1233) was found to be unaffected by non-specific inhibitor in human serum and, hence, the sera tested with this virus were not given cholera-filtrate treatment.

#### *Viral antigens*

Antigens were prepared from strains of virus selected as representative of the various known types and subgroups of the agents of human influenza (van der Veen & Mulder;<sup>50</sup> Burnet;<sup>4</sup> Isaacs;<sup>29</sup> Hilleman,<sup>19, 20</sup> WHO<sup>51</sup>). These were as shown in table I.

These viruses have been discussed previously (Hilleman et al.<sup>19, 22</sup>) and have been used as prototypes for earlier strain-analysis studies

**TABLE I. STRAINS OF VIRUS USED FOR PREPARING VIRAL ANTIGENS**

Virus type	Subgroup name	Test viruses employed	
		strain	year isolated
A	WS	WS	1933
A	PR8	PR8	1934
A	A-prime	FM1	1947
A	A-prime (contemporary)	FW-1-50	1950
B	Lee	Lee	1940
B	Warner (synonym Bon)	IB1	1950
C	1233	1233	1947

(Hilleman<sup>19</sup>). The antigens were prepared by methods already described (Hilleman et al.<sup>21</sup>) and were preserved in the dried state until used.

### *Test procedure*

The haemagglutination-inhibition titrations conformed to the technique of the Standard Reference Test in Influenza Diagnostic Studies (Committee on Standard Serological Procedures<sup>8</sup>). Type "O" human red blood-cells were employed in all tests. With influenza A and B viruses, the tests were read after the sera had stood for 55-60 minutes at room temperature. In the tests with influenza C, the sera were incubated in the refrigerator at 4°C for 60-65 minutes. Care must be taken in the reading of tests with low dilutions of treated serum because the characteristic shield pattern of haemagglutination is not always present. In such sera which are free of antibody, floccules of agglutinated cells may be formed which slide towards the bottom of the tube. Unless the tests are carefully observed, they may be interpreted erroneously as negative agglutination.

The titre of each serum was read as the highest initial dilution of serum which gave definite inhibition of haemagglutination. The antibody level of each group of sera tested was expressed as the geometric mean of the titres of the individual sera in the group. Differences in antibody level were considered significant if they were more than twice their standard error.

## **Findings**

As might be expected, the antibody levels of the individual sera against any particular virus showed a considerable variation, and it was not until the mean levels of the groups were calculated and compared that the epidemiological pattern became clear. In the body of the report only the mean antibody levels for the various groups will be considered. However, illustrative examples of the amount of individual variation found are given in Annexes 1 and 2 (see pages 627 and 628). The mean antibody levels against the influenza A, B, and C viruses in sera collected in 1951 from persons of various ages are summarized in table II. The results of similar tests with the sera collected in the years 1943-51 from adults are given in table III. These data are presented graphically and discussed in the subsequent sections of the paper.

### *Influenza A*

*Age-specific antibody levels.* The mean antibody levels against the various subgroups of influenza A of those persons bled in 1951 are shown by age in graphic form in fig. 1. The differences in the antibody patterns of the A and A-prime viruses are quite striking. Antibody levels against

**TABLE II. MEAN ANTIBODY TITRES \* OF SERA OBTAINED IN 1951 FROM PERSONS OF VARIOUS AGES**

Age (years)	Number of sera	A		A-prime		B		C	
		WS	PR8	FM1	FW-1-50	Lee	IB1	number of sera	1233
geometric mean of titres									
< 1/2	7	2	13	1	6	9	2	0	—
1-2	16	0	2	2	9	2	2	6	4
3-5	31	2	7	15	41	7	2	27	63
6-8	30	2	7	44	64	6	3	24	89
9-11	25	2	10	68	52	10	8	10	121
adult	74	32	118	43	46	56	44	33	204

\* Titres expressed as denominator of serum dilution

**TABLE III. MEAN ANTIBODY TITRES \* OF GROUPS OF ADULTS, FREE FROM ACTIVE RESPIRATORY DISEASE, OBTAINED EACH YEAR: 1943-51**

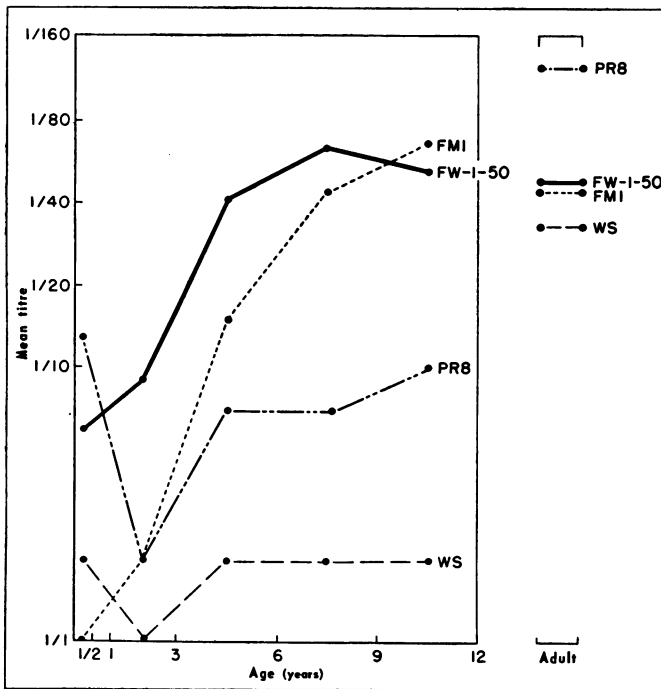
Year	Number of sera	A		A-prime		B		C	
		WS	PR8	FM1	FW-1-50	Lee	IB1	number of sera	1233
geometric mean of titres									
1943	35	9	18	3	5	10	7	32	263
1944	33	21	78	6	8	9	11	33	182
1945	33	14	65	13	8	24	20	33	129
1946	35	21	96	14	8	71	62	33	191
1947	32	28	91	18	20	65	49	33	159
1948	33	35	96	25	21	47	41	33	162
1949	35	23	83	18	21	59	39	33	219
1950	34	28	60	18	30	38	35	33	200
1951	75	32	118	43	46	56	44	33	204

\* Titres expressed as denominator of serum dilution

the A-type PR8 virus were very low in children under 12 years of age, in contrast with a high level in the adult population. Only one group of children showed a mean antibody titre of over 1/10. This was the group of infants under six months of age who had a mean titre of 1/13 against the virus. This antibody was, in all probability, acquired from the mother since it was not found in children between one and three years of age. The pattern of the WS antibody was similar to that for PR8, but the mean titres were much lower. There was almost no antibody against this virus in any of the children's sera, but a mean titre of 1/32 was obtained in adults.

In contrast with this, the antibody for both the A-prime strains FM1 and FW-1-50 rose from almost zero at under six months of age to a peak at 6-11 years. The adult levels of both FM1 and FW-1-50 were no higher than those found in children over six years of age. All children had more antibody against the A-prime than against the A strains.

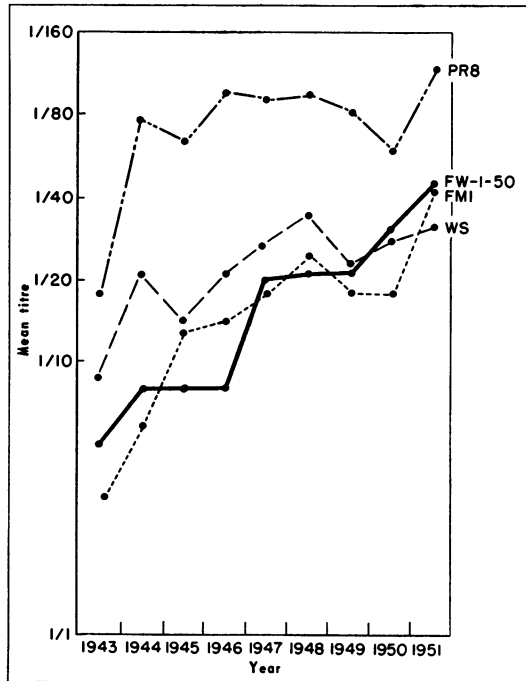
**FIG. 1. AGE-SPECIFIC MEAN ANTIBODY LEVELS AGAINST INFLUENZA A VIRUSES FOUND IN SERA OF PERSONS BLED IN 1951**



*Annual sampling of adult sera, 1943-51.* The changes from year to year in the antibody level of adults against the A-type viruses are shown in fig. 2. As with the age-specific levels, marked differences are noted in the antibody pattern against the A and A-prime viruses. Antibody against PR8 virus increased significantly between the times when the 1943 and the 1944 sera were drawn, and thereafter remained relatively constant at a high level without significant variation for the remaining eight years. The curve for the WS antibody paralleled, and roughly maintained half the height of, that for the PR8 strain. The only notable divergence from this general trend was the fact that, in addition to the 1944 increase in antibody, there was a significant increase in the WS level between 1945 and 1947.

Antibody against both the A-prime strains increased steadily from inconsequential levels in 1943 to mean titres of 1/43 and 1/46 in 1951. These rises were characterized by significant increases against FW-1-50 in 1947 and in 1950-1. A similar rise was found in the FM1 antibody in 1944-5 and in 1951. It may be noted that, despite progressive annual increases in antibody levels against the A-prime viruses, it was not until 1951 that values approaching those for PR8, or surpassing those for WS, were reached.

**FIG. 2. MEAN ANTIBODY LEVELS OF ADULTS AGAINST INFLUENZA A VIRUSES FOUND BY ANNUAL SAMPLING, 1943-51**



*Discussion.* The findings described above are consistent with, and tend to confirm, our knowledge of the prevalence of the different types of A virus among the population of the USA. Thus, PR8 virus was isolated in 1934 (Francis<sup>11</sup>) and is representative of the A-type viruses commonly recovered over the ensuing ten years (Hilleman;<sup>19</sup> Magill & Jotz;<sup>35</sup> van der Veen & Mulder<sup>49</sup>). The latest epidemic attributed to this type virus occurred in the winter of 1943-4 (Collins & Lehmann;<sup>7</sup> Commission on Acute Respiratory Diseases;<sup>48</sup> Francis<sup>13</sup>) and the strain has seldom been recovered since that date (Lépine et al.;<sup>32</sup> Nagler et al.;<sup>37</sup> van Rooyen et al.<sup>39</sup>). This



distribution in time has resulted in an adult population with considerable past exposure to PR8 and a childhood population with little or no evidence of contact with this virus. Consequently, we find high antibody levels in adults and almost no antibody in children born since 1944. It is noted also that the latest significant augmentation of PR8 antibody in adults occurred after the epidemic in 1943-4. There are several possible explanations for the steady high PR8 antibody level maintained in adults since 1944 despite the apparent infrequency of the virus in the community. Perhaps homologous influenza antibody levels persist in persons for long periods of time. However, a more likely explanation would seem to be one involving an anamnestic response to antigenic components which are common to PR8 and A-prime viruses but which represent only a minor portion of the mosaic of the latter.

The A-prime viruses, on the other hand, have been predominant at least since 1946 (Anderson;<sup>1</sup> Chu et al.;<sup>6</sup> Hilleman;<sup>19</sup> Isaacs et al.;<sup>30</sup> Magill & Jotz;<sup>35</sup> van der Veen & Mulder<sup>50</sup>) but were not prevalent before that time. The FMI strain was isolated in 1947 (Rasmussen et al.<sup>39</sup>), while FW-1-50 was recovered in 1950 (Hilleman et al.<sup>23</sup>) and represents the contemporary A-prime virus. Epidemics of influenza ascribed to A-prime strains have occurred in the USA in the late winters of 1947 (Collins & Lehmann;<sup>7</sup> Francis et al.;<sup>17</sup> Rasmussen et al.;<sup>38</sup> Sartwell & Long;<sup>42</sup> Sigel et al.<sup>43</sup>), 1950 (Collins et al.;<sup>7</sup> United States, Influenza Information Center<sup>49</sup>), and 1951 (Collins et al.;<sup>7</sup> Davis<sup>9</sup>). Such a known distribution of A-prime viruses can be readily correlated with the data illustrated in fig. 1, which indicate that children over six years of age and adults have similar antibody levels against these agents.

The occurrence of the A-prime epidemics in 1947, 1950, and 1951 is reflected in the levels of the adult sera. This is particularly true of the antibody against FW-1-50. It may be noted in fig. 2 that the antibody rise against FMI began as early as 1945, and this may indicate the presence of this type virus at least one year before the strain was isolated.

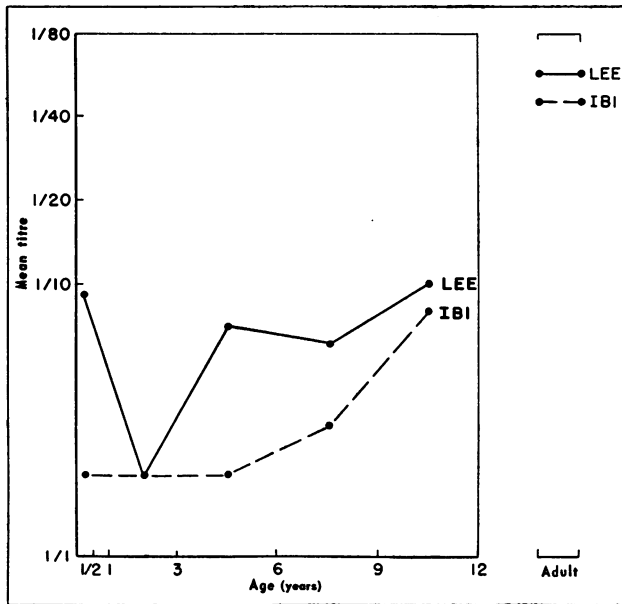
The WS strain was isolated in England in 1933 (Smith et al.<sup>44</sup>) but has not been known to be prevalent since that time. Because this was the first strain of human influenza virus to be isolated, nothing is known of when it first appeared or how long it had been present. The almost complete absence of antibody against this strain in children and the comparatively low levels in adults may be ascribed to the long interval that has elapsed since this virus has been known to be prevalent.

### *Influenza B*

*Age-specific antibody levels.* The antibody levels against the Lee and IB1 types of influenza B of persons bled in 1951 are shown, by age, in fig. 3. The mean titre of the children's sera against either of these viruses

never exceeded 1/10, indicating little exposure of the population under 12 years of age to these strains. In adults the antibody reached titres of 1/44 and 1/56.

FIG. 3. AGE-SPECIFIC MEAN ANTIBODY LEVELS AGAINST INFLUENZA B VIRUSES FOUND IN SERA OF PERSONS BLED IN 1951

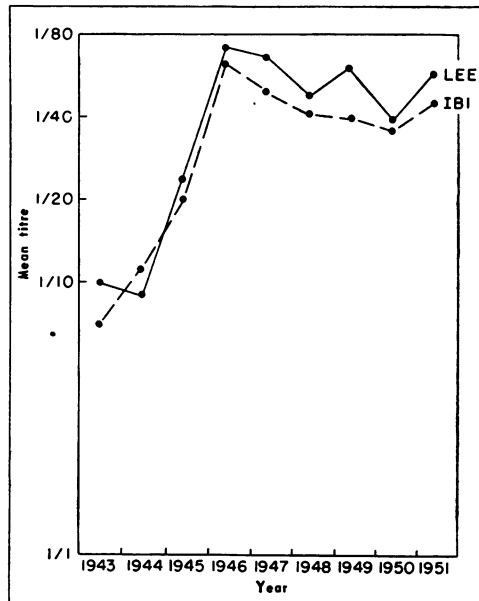


*Annual sampling of adult sera, 1943-51.* The yearly fluctuation in the antibody level of adults against influenza B is illustrated in fig. 4. These sera showed low levels in 1943 and 1944, and significant increases in 1945 and 1946; thereafter, the mean titres were maintained at levels between 1/35 and 1/65.

*Discussion.* The Lee virus was isolated in 1940 (Francis<sup>12</sup>) and is not known to have been prevalent since that time, whereas the IB1 virus (Tamm et al.<sup>45</sup>) was isolated in 1950 and is representative of the subgroup of B viruses which have been isolated since 1943 (Brans;<sup>3</sup> Burnet;<sup>4</sup> Hilleman et al.;<sup>19, 20, 22</sup> Magill et al.;<sup>35</sup> Tamm et al.<sup>45</sup>).

The serological patterns for B viruses, summarized in fig. 3 and 4, appear to be less closely related to the known epidemic prevalence of influenza B than are the periods and incidences of influenza A and A-prime, discussed earlier. The significant rise in B antibodies in 1946 and the subsequent maintenance of a high level in adults correlates with the 1945-6 epidemic (Collins & Lehmann;<sup>7</sup> Francis et al.;<sup>16</sup> Hirst et al.;<sup>27</sup> Kalter & Chapman<sup>31</sup>) and the intermittent prevalence of the virus since that time.

FIG. 4. MEAN ANTIBODY LEVELS OF ADULTS AGAINST INFLUENZA B VIRUSES FOUND BY ANNUAL SAMPLING, 1943-51



However, one wonders why the level remained in the neighbourhood of 1/10 during 1943 and 1944, only a few years after the 1940 epidemic of influenza B (Collins & Lehmann;<sup>7</sup> Eaton & Beck;<sup>10</sup> Francis;<sup>12</sup> Magill<sup>34</sup>), and why the antibody level increased significantly in 1945, one year before the 1945-6 epidemic. Moreover, the B antibody levels are relatively low in children of from 9 to 12 years of age who lived through the 1945-6 period. Certain observations may be considered in attempting to understand these aberrancies. These are concerned with the rather sporadic distribution of the disease, even during periods of prevalence of B virus and the relatively long periods between such episodes.

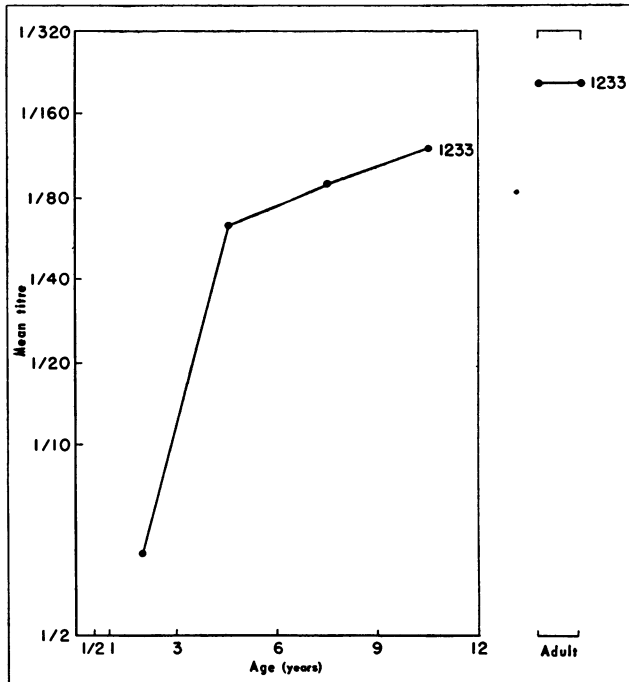
It is of interest that the antibody levels in human sera summarized in fig. 3 and 4 are similar for both strains. However, the two agents can be distinguished antigenically without difficulty in tests with animal sera (Hilleman et al.;<sup>19, 22</sup> Magill & Jotz;<sup>35</sup> Tamm et al.<sup>45</sup>). The findings of this investigation seem to indicate that in human serum the tests measured the same antibody in spite of the antigenic differences demonstrable by other methods.

### *Influenza C*

*Age-specific antibody levels.* The antibody levels against influenza C are shown by age in fig. 5. No sera were available from children of less

than six months of age at the time when the investigation referred to in fig. 5 was carried out. Subsequent tests performed on the sera of three infants aged between six weeks and three months gave titres of 1/20, 1/40,

**FIG. 5. AGE-SPECIFIC MEAN ANTIBODY LEVELS AGAINST INFLUENZA C VIRUS FOUND IN SERA OF PERSONS BLED IN 1951**

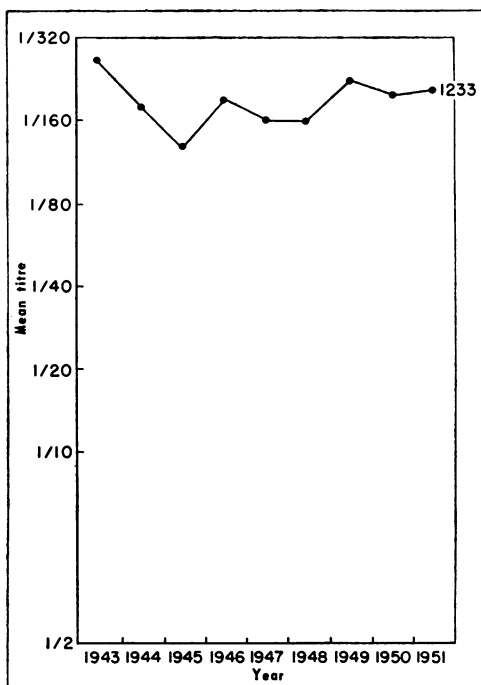


and 1/320; this antibody was probably of maternal origin. The antibody was at insignificant levels at from one to two years of age and then rose sharply to high levels at from three to five years. This high level was maintained throughout all the older age-groups.

*Annual sampling of adult sera, 1943-51.* The annual sampling of the adult sera shown in fig. 6 indicates a consistently high level of antibody throughout the nine years.

*Discussion.* Strain 1233, recovered from a case of respiratory disease in 1947 (Taylor<sup>46</sup>) was the first influenza C virus to be isolated. Its relation to clinical influenza was not clearly established until 1950 (Francis et al.<sup>15</sup>). Relatively few cases of this type of influenza have been reported to date, and few outbreaks have been described (Francis et al.;<sup>15</sup> Gerber et al.<sup>18</sup>). In spite of this, the antibody level for influenza C in sera of children over

**FIG. 6. MEAN ANTIBODY LEVELS OF ADULTS AGAINST INFLUENZA C VIRUS FOUND BY ANNUAL SAMPLING, 1943-51**



three years of age is high and indicates that infection occurs at an early age. Furthermore, the presence of large amounts of antibody in sera collected from adults in 1943 indicates that the virus was widespread in the population before that time. These findings are in agreement with those reported by Francis et al.<sup>15</sup> and support the concept that infection with this agent has been widespread in the population of this country for many years.

### General Discussion

These studies utilized the diagnostic haemagglutination-inhibition method for the survey of influenzal antibody in the population. The results of the tests with the influenza A and B viruses would not have been valid had not the sera been treated to remove non-specific inhibitor. Unpublished studies from this laboratory have shown that the PR8 virus employed in the tests was especially affected by the non-specific substance. Thus, it was observed that untreated sera from 16 children of from one to two years of age had a mean titre value of 1/160 with PR8; these same sera failed to give significant

inhibition of haemagglutination after cholera-filtrate treatment. The WS, FM1, Lee, and IB1 strains were also markedly affected by the non-specific substance, but to a somewhat less extent; the FW-1-50 agent was relatively unaffected, and the 1233 strain of influenza C virus was not influenced by the inhibitor.

In this study, the measurement of influenzal antibody in population groups was applied to the retrospective determination of influenza virus occurrence. It is not unreasonable to expect that the same approach may be useful in predicting the susceptibility of a population to a particular virus. This method might have been utilized at the time the first A-prime virus, Cam, was isolated in Australia in 1946 (Anderson<sup>1</sup>). Cam virus is essentially identical, antigenically, with the A-prime FM1 virus recovered in the USA the following year. As shown in table III, the mean titre in adults for the FM1 virus in 1946 was only 1/14. This level was considerably below that for the A strains occurring previously, and studies of this type would have suggested the susceptibility of the population to this kind of virus. Findings of this kind, if confirmed by a larger sampling of a representative group of persons, together with the results of the strain analysis studies, would suggest a need to include a newly isolated virus in the vaccine before the occurrence of an epidemic.

While the measurement of influenzal antibodies may provide a valuable yard-stick for estimating susceptibility of a given population to a given virus, it should be noted that the relationship between antibody titre and immunity is not always consistent. Thus, it has been shown in studies of naturally and experimentally induced influenza that the disease sometimes occurs in persons with high antibody levels, and that persons with low titres may escape infection (Francis et al.;<sup>14</sup> Rickard et al.;<sup>40</sup> Salk et al.<sup>41</sup>). It would appear, then, that other factors in addition to circulating antibody may be of importance in the immunology of this disease.

**ANNEX 1. ANTIBODY TITRES \* AGAINST INFLUENZA VIRUSES  
IN SERA COLLECTED IN 1951 FROM CHILDREN BETWEEN THREE AND FIVE  
YEARS OF AGE**

Serum no.	Type A		Type A-prime		Type B		Serum no.	Type C (1233)
	WS	PR8	FM1	FW-1-50	Lee	IB1		
38	0	10	0	10	0	0	6	10
80	10	20	80	160	10	10	10	320
122	0	10	40	40	0	0	14	320
123	20	40	160	160	40	0	16	40
126	0	0	0	0	0	0	23	320
141	20	80	160	160	20	0	25	320
147	—	—	—	20	10	0	26	320
155	0	0	0	10	0	0	31	80
167	0	0	0	10	0	0	32	10
171	0	10	10	20	20	0	33	160
178	0	0	80	160	0	0	34	320
179	0	0	320	640	10	0	36	0
180	0	10	320	640	20	0	37	20
185	0	0	0	0	0	0	38	40
186	0	40	0	40	40	0	39	80
192	0	10	160	320	0	0	41	40
194	20	40	640	320	40	10	44	20
195	0	0	160	80	10	40	53	160
196	0	20	320	320	20	20	55	320
197	0	20	0	20	20	0	62	160
198	0	0	0	10	20	0	63	80
199	0	20	160	160	20	0	66	20
210	0	0	80	80	0	0	72	10
215	0	0	0	20	20	0	77	10
216	0	0	0	20	10	0	78	160
219	20	40	0	20	40	10	81	10
220	10	20	40	40	20	10	86	640
222	0	20	40	40	0	0		
228	10	20	0	0	20	0		
232	20	40	320	320	20	0		
249	0	20	0	20	20	0		

\* Titres expressed as denominator of serum dilution

**ANNEX 2. ANTIBODY TITRES \* AGAINST INFLUENZA VIRUSES  
IN SERA COLLECTED FROM ADULTS IN 1950**

Serum no.	Type A		Type A-prime		Type B		Serum no.	Type C (1233)
	WS	PR8	FM1	FW-1-50	Lee	IB1		
253	0	0	0	20	20	40	22	40
254	80	160	40	40	80	80	23	40
351	160	320	80	80	20	20	24	160
352	80	320	40	40	160	80	49	320
355	40	160	20	20	320	160	50	320
356	40	160	40	10	20	20	51	320
357	10	40	20	20	40	40	76	160
358	160	160	80	20	160	160	77	80
359	40	80	10	40	40	80	78	40
360	40	40	10	10	20	40	103	640
361	40	80	20	20	0	20	104	160
362	20	160	320	80	80	160	105	320
363	40	160	80	20	20	40	130	320
364	20	20	0	20	80	80	131	640
365	20	80	80	80	20	20	132	640
366	10	20	20	20	40	10	157	640
367	20	40	40	20	80	40	158	80
368	40	80	40	40	40	40	159	320
369	160	160	40	20	160	80	184	320
370	160	320	20	160	80	80	185	320
371	10	20	10	10	40	40	186	80
372	0	0	0	20	0	0	211	640
373	160	320	40	20	320	320	212	640
374	160	160	80	80	80	80	213	640
375	20	40	20	20	320	40	238	160
376	0	0	0	40	10	0	239	320
377	20	320	160	160	80	80	240	320
378	20	80	80	40	20	20	265	20
379	0	0	0	20	0	0	266	40
381	160	80	20	80	80	80	267	40
382	10	80	0	0	10	10	292	320
383	160	320	40	80	160	80	293	160
384	20	40	0	20	40	40	294	640
385	160	320	80	80	20	20		

\* Titres expressed as denominator of serum dilution



## ACKNOWLEDGEMENTS

We wish to thank Corporal D. H. Roenisch for performing the statistical computations. The technical assistance of Corporal T. Courtenay is also gratefully acknowledged.

## RÉSUMÉ

Dès le début des études sur l'infection grippale, on s'est rendu compte que l'immunologie de la grippe reposait sur les mêmes principes que celle d'autres maladies infectieuses et qu'il existait un rapport entre le taux des anticorps suscités dans le sérum par le virus et la résistance du sujet à la maladie. Il devenait possible dès lors, en analysant les sérums de groupes représentatifs de la population, de recueillir des informations sur la nature des infections passées et sur la répartition des virus grippaux.

Les sérums qui ont fait l'objet de cette étude ont été prélevés, chaque année depuis 1943, sur des adultes, membres du personnel militaire des Etats-Unis, et leurs proches, et, en 1951, sur des sujets d'âges divers. Les antigènes ont été préparés à partir des divers types et sous-groupes de virus humains. Des hématies humaines de groupe sanguin 0 ont été employées pour les tests d'hémagglutination.

Les résultats des analyses sérologiques ont concordé, dans les grandes lignes, avec les connaissances que l'on possédait sur la répartition des divers virus A dans la population des Etats-Unis. Le virus PR8, isolé en 1934, fut actif durant les dix années qui suivirent; la dernière épidémie due à ce virus date de 1943-44. Les résultats des analyses sérologiques confirment ces faits : la population adulte, exposée longtemps à l'infection, présente des niveaux d'anticorps élevés, tandis que les enfants nés depuis 1944 ne possèdent pratiquement pas d'anticorps correspondant à cette souche. Depuis 1946, les virus A-prime ont prédominé, fait confirmé par l'analyse des sérums. On constate toutefois que l'augmentation du taux des anticorps anti-A-prime s'est manifestée dès 1945 déjà; il semble donc que cette souche ait existé une année avant d'être reconnue et isolée.

La souche WS, isolée en 1933, n'a guère été retrouvée depuis lors chez les sujets atteints de grippe, et l'on ignore tout de son activité avant cette date. La longueur de la période durant laquelle ce virus n'a manifesté aucune activité permet peut-être d'expliquer le niveau très faible des anticorps anti-WS chez les adultes et leur absence quasi complète chez les enfants.

Les observations faites sur les anticorps du groupe de virus B sont moins nettes que celles faites sur les anticorps A. On constate des fluctuations, difficiles à interpréter. C'est ainsi qu'en 1943 et 1944, c'est-à-dire quelques années seulement après l'épidémie de 1940, le taux est faible, alors qu'il accuse une augmentation sensible en 1945, avant l'épidémie de 1945-46.

Les manifestations épidémiologiques de la grippe C, souche 1233, isolée en 1947, ont été rares et les cas peu nombreux. Cependant, on a trouvé des taux d'anticorps significatifs, probablement d'origine maternelle, chez des enfants de six semaines à trois mois. Une brusque élévation du taux a été observée chez les enfants de trois à cinq ans, un taux élevé existant également dans les groupes d'âge supérieurs. Il semble que l'infection C, bien que peu répandue, survienne chez les enfants en bas âge. Le niveau élevé des anticorps chez les adultes à partir de 1943 indique que le virus était répandu dans la population avant cette date.

La détermination du taux des anticorps vis-à-vis d'un type de virus peut donner une indication de la résistance d'une population, mais le rapport entre le titre d'anticorps et l'immunité n'est pas constant. Des personnes ayant un titre élevé peuvent contracter l'infection et d'autres, ayant un titre faible, y échapper. Il semble donc que d'autres facteurs interviennent dans l'immunité contre cette maladie.

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